

Presentation 15 – Lea Steele

**Highlights of Recently
Published Research**

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Recently-published research

- Health effects of Gulf War-related exposures
 - Human/occupational studies
 - Animal studies
- Epidemiologic studies of Gulf War veterans
- Multisymptom illnesses: treatments

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**Health Effects of Gulf War-related Exposures:
Human studies**

Paraoxonase polymorphisms and self-reported ill health in farmers dipping sheep.
Povey et al. *Occup Med Jun 2005 55:282*

- PON1 192 Q form more efficiently hydrolyzes diazinon, sarin than R form; PON1 55 polymorphisms affect PON1 activity levels
- This study evaluated 409 U.K. farmers: 'cases' had chronic symptoms they attributed to sheep dip, referents did not
- Homogenous population generated by eliminating subjects with identified diseases or injuries that could explain their symptoms
- Confirmed previous findings that sheep dippers with chronic symptoms are significantly more likely to carry R allele at position 192 (RR and QR genotypes)
- Sheep dippers with chronic symptoms also significantly more likely to be LL homozygotes at position 55 (than LM or MM)
- Support hypothesis that OPs contribute to the chronic ill health of sheep dippers

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**Health Effects of Gulf War-related Exposures:
Human Studies**

Neurologic symptoms in licensed private pesticide applicators in the agricultural health study. Kamel et al. *Environ Health Perspec Jul 2005 113:877*.

- High-level pesticide exposure associated with acute, chronic neurological problems; little known about lower-level exposures
- Agricultural Health Study collected neuro symptom and lifetime exposure information on 18,782 licensed pesticide applicators
- Number of days of insecticide use was significantly associated with greater number of symptoms, in a dose response fashion
- Among insecticides, greatest effect from organophosphates, organochlorines
- Effects persisted after eliminating all individuals with history of pesticide poisoning, excess exposure incident

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Effects of Gulf War-related Exposures: Animal Studies

Vaccination alone or in combination with pyridostigmine promotes and prolongs activation of stress-activated kinases induced by stress in the mouse brain. Wang D et al, *J Neurochem* May 2005 93: 1010.

- Previously reported that variety of stressors induce activation of protein kinases in the brain (immune activation, potential CNS regulation)
- Immunization with KLH (a vaccine adjuvant) produced modest increase in kinase activation with stress, but prolonged the effect
- PB alone did not activate kinases, but significantly prolonged kinase activation induced by stress+vaccination, induced marker of neuro injury
- Concluded that combination of PB, vaccines, and stress act synergistically to produce kinase-mediated brain damage

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Effects of Gulf War-related Exposures: Animal Studies

Pyrethroid pesticide-induced alterations in dopamine transporter functions
Elwan et al. *Toxicol Appl Pharmacol* Jul 2005 (Epub)

- Study found that repeat exposure of mice to pyrethroids increases dopamine uptake mediated by DAT ; longer-term cell exposure results in decrease dopamine uptake, apoptosis
- Conclude that upregulation of DAT by permethrins may increase the susceptibility of dopamine neurons to toxic insult by other neurotoxins

Neuromechanical effects of pyrethroids, allethrin, cyhalothrin and deltamethrin on the cholinergic processes in rat brain. Hossain et al, *Life Sciences* Jul 2005, 77: 795

- Previous studies have indicated that pyrethroids differentially modulate acetylcholine release in the brain
- This study found that pyrethroids significantly increase levels of ACh synthesizing enzyme choline acetyltransferase, and altered uptake of choline
- Demonstrate mechanisms of pyrethroid effects on cholinergic system

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Epidemiologic Studies Gulf War Veterans

Gulf War Veterans' Health: medical evaluation of a U.S. cohort.
Eisen et al, *Ann Intern Med* Jun 2005 142: 881.

- Clinical evaluations from Phase III of VA's large national study of Gulf War era veterans and their families
- Clinical evaluations of 1061 Gulf War veterans and 1128 nondeployed era veterans in 16 VAMCs
- Compared 12 predefined health outcomes in both groups
- Mean SF-36 PCS was 49.3 for deployed, 50.8 for nondeployed

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Epidemiologic Studies: Gulf War Veterans

	Prev. in Gulf Veterans	Prev. in Non-Gulf	Adj. OR
<i>Fibromyalgia</i>	2.0%	1.2%	2.3*
<i>CFS</i>	1.6%	0.1%	40.6*
<i>Skin conditions</i>	34.6%	26.8%	1.4*
<i>Dyspepsia</i>	9.1%	6.0%	1.9*
<i>Hypertension</i>	9.1%	12.6%	ns
<i>Hepatitis</i>	6.5%	5.2%	ns
<i>Symptomatic arthralgias</i>	6.4%	6.8%	ns
<i>Obstructive lung disease</i>	4.5%	5.9%	ns
<i>Diabetes mellitus</i>	4.2%	3.5%	ns
<i>Peripheral neuropathy</i>	4.8%	5.9%	ns
<i>Hypothyroidism</i>	1.6%	1.2%	ns

*p<0.05

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Epidemiologic Studies Gulf War Veterans

Interpretation of results may vary....

- Paper concludes: "Ten years after the Gulf War, the physical health of deployed and nondeployed veterans is similar"
- Presentation of results at IOM meeting also suggested that the health of Gulf veterans similar to nondeployed; Gulf veterans don't have much of a problem
- Results interpreted by VA scientist as demonstrating a significant, clinically validated problem in Gulf veterans (CFS)

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Epidemiologic Studies Gulf War Veterans

Major concern re: study approach: Choice of Outcomes

- Results generally validated results from initial survey, i.e. CFS, skin conditions elevated; hepatitis, diabetes, hypertension not elevated
- No evaluation of Gulf War-related multisymptom illnesses, consistently-identified primary problem in Gulf War veterans
- No evaluation of rates of diagnosed conditions thought to be elevated in Gulf War veterans: e.g., migraines, sleep disorders

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Epidemiologic Studies Gulf War Veterans

Eisen et al, *Ann Intern Med* Jun 2005 142: 881.

Summary:

- CFS, FM, skin conditions, dyspepsia significantly elevated in Gulf War veterans.
- CFS dramatically increased (OR = 40.6) but affects only 1.6% Gulf War veterans.
- Physical health summary score similar in Gulf veterans, nondeployed (both ~50)
- Unclear why study did not address central research questions related to health of Gulf War veterans

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Epidemiologic Studies Gulf War Veterans

Biological monitoring and surveillance results of Gulf War I veterans exposed to depleted uranium. McDiarmid et al, *Int Arch Occup Environ Health* Aug 2005 [Epub]

- Reports on physical exams and lab evaluations of 32 Gulf veterans with embedded DU shrapnel, exams provided biannually
- Fifth of biannual evaluations provided to this cohort (done in 2003)
- Found that urine uranium continues to be elevated in this cohort 12 years after first exposure
- Paper concludes that "no clinically significant uranium-related health effects were observed in blood count, blood chemistries, neuropsychological measures, semen quality, or genotoxicity measures."

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Epidemiologic Studies Gulf War Veterans

McDiarmid et al, *Int Arch Occup Environ Health* Aug 2005 [Epub]

- > Among cohort of 32 veterans, measures were compared between 13 veterans with "high level" urine uranium (>0.10 ug/g creatine) and 19 with lower levels of urinary uranium (<0.10 ug/g creatine)
- > Significant differences reported include:
 - Serum phosphate levels (high)
 - Uranium levels sign assoc with neurocogn accuracy index (intellectual level)
- > Differences approaching significance include:
 - Urine retinol binding protein (high)
 - Neurocognitive accuracy measure (more impairment)
 - Mutation frequencies
- > Low and high U groups had elevated serum prolactin levels

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Epidemiologic Studies Gulf War Veterans

McDiarmid et al, *Int Arch Occup Environ Health* Aug 2005 [Epub]

- Concerns:
 - > Comparisons between "low urine uranium" and "high urine uranium" groups, not between those with/without uranium, or exposed/not exposed
 - > Small sample limits ability to detect significant differences
 - > Differences that are identified are minimized
 - > No information on chronic symptoms, symptom complexes
 - > No information on tumors

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Multisymptom Illnesses Treatment Studies

Effect of aerobic exercise on patients with primary fibromyalgia. Salek et al, *Mymensingh Med J* Jul 2005, 14: 141.

- 68 adult patients, 2 groups: tricyclic antidepressants+analgesics with/without aerobic exercise
- Treatment 16 weeks; outcomes evaluated include pain severity, # trigger points, sleep regularity, global physician evaluation
- Results:
 - 48% improved with exercise
 - 39% improved without exercise
- Difference not significant

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Multisymptom Illnesses Treatment Studies

A randomized clinical trial of an individualized home-based exercise programme for women with fibromyalgia. DaCosta et al, *Rheumatology* Jul 2005 [Epub]

- 79 women with FM, 2 groups: individualized, moderate home-based exercise, usual care
- Treatment 12 weeks; outcomes evaluated FM-specific global health status instrument score, pain intensity score, SCL-90 (psych distress)
- Sign improvement in global health, upper body pain
- No sign differences in lower body pain, psych scores
- Improvements maintained at 3 month and 9 month follow up

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Multisymptom Illnesses Treatment Studies

A randomized controlled trial of dehydroepiandrosterone in postmenopausal women with fibromyalgia. *J Rheumatol* 2005 Jul;1336

- 52 patients with FM, cross-over study
- 3 mos treatment with 50 mg. DHEA (adrenal hormone)
- No significant improvement in pain, fatigue, cognitive function

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Multisymptom Illnesses Treatment Studies

Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Crofford LJ et al, *Arthritis Rheum* Apr 2005, 52:1264.

- 529 patients, 8 week treatment
- Pregabalin (analgesic, antianxiety, anticonvulsant)
- 450 mg/day Pregabalin sign reduced pain scores; sign improvement in sleep measures, fatigue
29% of treatment grp had $\geq 50\%$ improvement in pain;
13% placebo

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Multisymptom Illnesses Treatment Studies

A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Homan et al, *Arthritis Rheum* Aug 2005 52:2495

- 60 patients with FM
- 14 week treatment with pramipexole (dopamine agonist)
- Sign improvements in FM impact score, function, fatigue
- 42% of treatment group had $\geq 50\%$ decrease in pain score;
14% placebo

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